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R C van Dijk

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Anmelder/Applicant(s)/Demandeur(s):

Cilag AG
Hochstrasse 207
8205 Schaffhausen
SUISSE

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Spherical pellet formulations

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Spherical Pellet Formulations

Brief description of the invention

This invention relates to spherical pellets containing a water-soluble drug, which pellets may be coated, and to sustained release oral dosage forms containing said pellets. The invention further relates to a process for preparing said pellets based on the use of a dry lubricant.

Background of the Invention

Many pharmaceutical formulations come in single dosage unit forms, which allow the administration of discrete amounts of the active ingredient. The most frequently used unit dosage form without doubt is a tablet. In a number of instances there exists a need for higher or lower doses than the standard amount that is released upon administration of a single unit dose. In case of higher doses, several of the dose units can be administered or if lower doses are required the unit dosage form can be split, e.g. a tablet can be broken in half.

In a number of instances it may be required to administer the active ingredient in varying doses that do not fit into this pattern. This can for example be necessary for active ingredients that have to be administered in very specific quantities, e.g. quantities that are highly dependent upon the patient population at which they are aimed, or quantities that have to be adjusted in terms of weight, sex or age of the patient. In such instances it may be appropriate to use variable dosage forms or multi-unit dosage forms such as capsules or sachet. These dosage forms contain the required amounts of the active ingredient formulated in an appropriate carrier.

Obvious formulations for use in capsules or sachets are powdery formulations. However, it is not always possible or desirable to use powdery formulations for this purpose. The active ingredient may for example be too aggressive to the stomach or other parts of the gastro-intestinal system or may be prone to decomposition by gastric juices. In such instances the active ingredient needs to be kept separated from environmental factors by a suitable technique such as coating, e.g. by coating of granules, or by incorporation into pellets or beads. The latter in turn may also be coated for example, to provide further protection, for taste masking, or for affecting the release of the active ingredient.

Quite a number of active ingredients require specific release kinetics or prolonged release. In such instances use is made of so-called sustained or controlled release formulations.

Controlled release formulations have been introduced for active ingredients that require a specific release pattern such as a constant release during a certain period of time, i.e. a release of the active ingredient that is devoid of peaks or drops. A variety of controlled release formulations are now available that avoid temporary over- or under-dosing of the active ingredient.

Sustained release formulations have been developed in which the release of the active substance is prolonged in some way in order to maintain therapeutic activity for a longer period of time.

Sustained release formulations typically are applied for drugs that have a short half-life or for active ingredients that require active blood plasma levels for long periods of time. In the former instance, multiple daily dose regimens can be avoided such as b.i.d., t.i.d. or q.i.d regimens, which often lead to problems caused by lack of patient compliance. Sustained release formulations are also applied for patients on chronical medication where one administration suffices to keep active blood plasma levels for longer periods such as several days or even weeks.

However, the term 'sustained release' is often also used for formulations that show controlled release during a prolonged period of time.

Also in the instance of sustained or controlled release formulations, the active ingredient can be incorporated into pellets, which may be coated with a suitable coating material that affects the release pattern of the active ingredient.

In order to have a regular and controllable release it is required that the pellets come in regular shapes, more in particular as regularly shaped spheres. An important factor that governs the release of an active from a pellet is the amount of the surface that is in contact with the medium to which the active ingredient is released. Irregularly shaped pellets will have irregular surfaces and concomitant releases of the active. Release of the active is better controllable with regularly shaped pellets.

A further advantage of spherically shaped pellets is that they are more easily coated and moreover that the thickness of the coating is more uniform when the pellets have regular round shapes. This is even more the case when the size distribution of the pellets is narrow.

Still another advantage associated with spherically shaped pellets is their ease of handling and filling into capsules, sachets or other application forms such as bottles.

As a further reason to prefer coated multi-unit dosage forms over coated single-unit dosage forms such as coated tablets, is the risk of dose dumping. This phenomenon occurs when there are undesired openings in the coating, which may be caused during manufacturing or by the patient while handling the dosage form or unvoluntary chewing on it. Small openings or cracks in the coating mantle causes contact of the interior with body fluids setting the release of the active in motion. The amount of active released in case of a single unit dose evidently will be much higher than with a multi unit dosage form such as a pellet.

One way to produce such spherically shaped pellets is by adding water to a dry blend of active ingredient and a suitable carrier and the wet mass is extruded through a small

orifice (typically approx. 1 mm). The water acts as a lubricant during this process and reduces the friction and heat generated during extrusion. The extruded material is placed into a spheroniser where it is spun at high speed. During this step the extrudates break and round into pellets, the size being determined by the size of the extrusion orifice. The extrudate needs to be sufficiently moist to extrude, sufficiently dry to break and sufficiently moist to round without being too moist which results in congealing and sticking of the pellets. Essentially the moisture content of the wetted mass is critical.

When using this methodology, a number of active ingredients produce a sticky mass upon extrusion, which cannot be broken when spun at high speed. This seems to be the case when using water-soluble active ingredients. Apparently active ingredients behave as an additional binder in the mixture and prevent the extrudate from becoming broken and rounded when put in a spheronizer. The extrudate in this instance rounds into inhomogeneously sized pellets.

The amount of water required to enable extrusion of the dry blend is quite high. Upon spheronisation a densification of the pellets occurs and the excess water in the extrudate migrates to the pellet surface where it causes sticking of the pellets to the spheroniser walls and plate.

One particular example of an active ingredient that is water-soluble and produces a sticky mass when subjected to a wet extrusion procedure is the analgesic tramadol, which typically is used in its hydrochloride salt form. Tramadol hydrochloride is very water-soluble and upon dissolution produces a sticky solution. It behaves as an additional binder in the mixture and prevents the extrudate breaking when spun at high speed. The extrudate therefore rounds into inhomogenously sized pellets.

One of the problems associated with tramadol is that it has a relatively short half-life thus requiring a multiple dose regimen. Initial overdosing during the initial time period after administration may result in side effects whereas underdosing results in inefficacy so that the pain sensation may arise again. Overdosing problems may occur because tramadol hydrochloride is an orally active pure agonist opioid analgesic. Opioids have for many years been used as analgesics to treat severe pain. They, however, produce

undesirable side effects and, as a result, cannot always be given repeatedly or at high doses. However, clinical experience indicates that tramadol lacks many of the typical side effects of opioid agonists, e.g., respiratory depression, constipation, tolerance and abuse liability. Tramadol's 'atypical' combination of non-opioid and opioid activity makes tramadol a very unique drug.

It therefore is an object of the present invention to provide a method to produce spherically shaped pellets containing water-soluble active ingredient by extrusion and subsequent spheronization. It is a further object to provide pellets containing a water-soluble active ingredient of sufficient spherical homogeneity so that they can be coated resulting in coated pellets that can be used in sustained or controlled release applications. It is still a further object of this invention to provide coated pellets containing water-soluble drugs having a coating of homogeneous thickness. Another object is to provide pellets, in particular coated pellets, that have a narrow size distribution.

A further object of this invention is to provide sustained release dosage forms comprising pellets containing water-soluble drugs. A further object is to provide sustained release formulations of tramadol that release tramadol active during a sufficiently long period of time. In particular there is a need for formulations that release tramadol during 12 hours and preferably during 24 hours.

Further there is a need for sustained release formulations that release tramadol active in a controlled manner, i.e. without peaks or drops in its release pattern.

A further object of the present invention is to provide a method for treating conditions of pain, in particular severe pain, in mammals.

These objects are attained by the various aspects of the present invention. These in particular comprise the keeping low of the water content in the blend of excipients used in the extrusion process, in particular reducing the water content such that the blend is dry, which further comprise the replacing of water by a dry lubricant, allowing the

material to be extruded at a much lower moisture content thereby reducing the sticking observed in the spheroniser.

Summary of the invention

This invention relates to spherical pellets comprising a water-soluble active ingredient. The pellets of the invention can be for application in immediate release products or, in particular, for sustained release products.

In another aspect, this invention relates to spherical pellets comprising a water-soluble active ingredient, said pellets having a low water content.

In a further aspect, the invention relates to coated spherical pellets comprising a water-soluble active ingredient.

In still a further aspect, the invention concerns a pharmaceutical dosage form containing spherical pellets or a coated spherical pellets as described herein. A preferred such dosage form is a capsule filled with said pellets or coated pellets.

In still another aspect, the present invention concerns a sustained release oral pharmaceutical dosage form containing an effective amount of a water-soluble active ingredient, characterized in that the active ingredient is formulated into a spherical pellet, which has been coated with an appropriate sustained release coating.

In a preferred aspect of this invention, the active ingredient in the pellets is tramadol, or a pharmaceutically acceptable acid addition salt thereof.

In a more preferred embodiment, the invention relates to a sustained release oral pharmaceutical dosage form containing an effective amount of tramadol, or a pharmaceutically acceptable salt thereof, formulated into a spherical pellet, which

has been coated with an appropriate sustained release coating. Of particular interest are capsules containing pellets as defined herein.

The sustained release oral dosage forms of this invention are for administering to a human patient on a twice-a-day (b.i.d.) and in particular on a once-a-day basis.

In still another aspect the invention concerns a process for manufacturing spherical pellets as defined herein, said method comprising extruding a mixture of the active ingredient with a suitable carrier in the presence of a dry lubricant and spheronizing the extrudate, wherin the dry-lubricant is a triglyceride. In a preferred process the pellets are subsequently coated with a suitable coating.

In still another aspect, the invention concerns a process for manufacturing a pharmaceutical dosage from, said method comprising filling the pellets into a suitable container. In a preferred aspect the container is a capsule.

Furthermore, the invention concerns a method of treating a warm blooded animal suffering from analgesia, said method comprising the administration of an oral dosage form containing an effective amount of tramadol, said dosage form being as described herein.

Detailed description of the invention

Subject of the present invention are spherical pellets containing a water-soluble active ingredient. The pellets may further contain a suitable carrier and other optional ingredients. They may also contain a dry lubricant.

The term 'spherical pellet' is meant to comprise pellets, beads or spheroids that are more or less of regular shape. In particular embodiments of the invention the shape is round or about round, i.e. having or approaching the shape of a small sphere.

The average size of the pellets may vary but preferably the diameter is in the range of about 0.1 mm to 3 mm, in particular from about 0.5 mm to about 2 mm, more preferably about 1 mm.

The size distribution of the pellets may vary but in general it is preferred that it has limited variation. It may vary between within a range of 10 to 20%. The size distribution may vary in a statistical manner, i.e. in a bell-shaped curve wherein e.g. 90 % or e.g. 95 % of the number of pellets are within a size range that varies between about 10 % to about 20 % of the average sizes mentioned above.

The active ingredients incorporated into the pellets of this invention are water-soluble. Particular active ingredients are those forming a sticky mass upon contact with water and/or the other excipients used in the extrudate mixture. More in particular, the active ingredients used in the pellets according to this invention are those that act as an additional binder in the mixture that ia extruded and spheronised.

The active ingredient is present in an amount, which is in the range of from about 0.1 to about 50%, in particular from about 1 to about 40%, more in particular from about 10 to about 35%, w/w relative to the total weight of the pellet.

The pellets of the invention may further comprise an appropriate carrier which may be any carrier known in the art used for making pellets. Particular carrier materials are spheronising agents that may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form pellets. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, the product sold under the tradename 'Avicel'.

The spheronising agent is present in an amount, which is in the range of from about 25% to about 90%, %, in particular from about 35% to about 69%% w/w, relative to the total weight of the pellet.

Optionally the pellets may contain other pharmaceutically acceptable ingredients such as binders, bulking agents and colorants. Suitable binders, some of which may also contribute to the controlled release properties of the pellets, include water-soluble polymers, e.g. water-soluble hydroxyalkyl celluloses such as hydroxypropyl cellulose, or water insoluble polymers, such as acrylic polymers or copolymers, or alkyl celluloses such as, for example, ethylcellulose. Suitable bulking agents include lactose or colloidal silicon dioxide. The amount of these other ingredients in the pellets will be relatively small, e.g. lower than 30 %, or 20 %, or even lower than 10 % or 5 % w/w relative to the total weight of the pellet.

The pellets may also contain a dry lubricant. Apart from providing lubrication, the dry lubricant also allows the material to be extruded at a much lower moisture content thereby reducing the sticking observed in the spheroniser.

The dry lubricant in particular is a mono-, di- or triglyceride, or mixtures thereof. Suitable mono-, di- or triglycerides are the mono-, di- or triesters of glycerine and one or more fatty acids. The mono-, di- or triglycerides may contain the same or different fatty acid residues or mixtures thereof, e.g. technical mixtures obtained from saponification of natural oils. Of particular interest are fatty acid triglycerides wherin the fatty acid residue has from 12 to 30 carbon atoms and is saturated or partially unsaturated or may be substituted, e.g. with one or more hydroxy functions. Preferred are mono-, di- or triglycerides derived from C_{18-30} fatty acids, in particular derived from C_{22-26} fatty acids. Of particularly preferred interest are behenic acid mono-, di- or triglycerides.

The dry lubricant preferably is solid at room temperature and has a melting point or melting range which is in the range of 60 °C to 90 °C, in particular is in the range of 70°C to 80 °C.

A particularly suitable dry lubricant is the glyceride mixture sold under the trade name 'Compritol™ 888ATO' which is a mixture of glyceryl mono-, di- and tribehenate, the dibehenate fraction being predominant, and having a melting range of about 69 – 74 °C.

Preferably, the dry lubricant is selected such that it does not impact the dissolution behavior of the active ingredient.

The dry lubricant is present in an amount, which is in the range of from about 2% to about 50%, in particular between 10 % and 35 % w/w, relative to the total weight of the pellet.

The pellets according to the invention have a low water content. In particular embodiments, the water contents in the pellets is lower than 5%, more in particular lower than 3%, w/w relative to the total weight of the pellet.

The pellets according to the invention are made by an extrusion process followed by spheronization. The mixture used in the extrusion process comprises active ingredient, a suitable carrier material and other optional ingredients, and a dry lubricant. The amount of dry lubricant in this mixture may vary but in general is comprised between 10 % and 35 % (w/w). A small amount of water may be added to the mixture. In a particular execution, the amount of water is 5 % or lower, or 3 % or lower, or 1.5 % or lower, w/w, relative to the total weight of the mixture for extrusion.

The ingredients are mixed together in any given sequence. In one embodiment, the dry lubricant is added to a mixture of active ingredient and the carrier material at room temperature. The mixture is subsequently extruded through a small orifice. The diameter of the latter is in relation to the size of the pellets that are eventually produced from the extrudate. In one embodiment, the diameter of the orifices is in the range of 0.5 mm to 2.0 mm. The extrusion may be done at slightly elevated temperature but preferably is performed without applied heating.

The extrudated material is subsequently placed into a spheronizer where it is spun at high speed.

In a specific embodiment of the invention, the pellets are subsequently coated with a suitable coating using art known methods. The coating can either be a functional coating or a diffusion controlling coating.

A functional coating may be applied for e.g. taste masking, protection of the pellets, to have improved stability (shelf-life) or for identification (for example by coloring). Functional coating often will be film coating, using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Diffusion controlling coatings are designed to achieve a target release profile such as controlled or sustained release. Suitable controlled or sustained release coating materials include water-insoluble waxes and polymers such as polymethacrylates, for example the Eudragit™ polymers, or water insoluble celluloses, in particular alkyl celluloses such as ethylcellulose. Optionally, water-soluble polymers such as polyvinylpyrrolidone or water-soluble celluloses such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose may be included. Further components that may be added are water-soluble agents such as polysorbate. Of particular interest is ethylcellulose (EC). Preferably, a suitable plasticizer is added. A coating material that is particularly suitable is the coating material sold under the trade name Surelease™ (Colorcon), which is a dispersion of ethylcellulose.

In a particular embodiment, the active ingredient for use in the pellets according to the present invention is tramadol, which is the compound (1R,2R or 1S,2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol which belongs to a class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkylring, disclosed in U.S. Pat. No. 3,652,589. Preferably tramadol is used as a pharmaceutically acceptable salt form, in particular as its hydrochloride salt. Tramadol is commercially available from Gruenenthal or may be made by the process described in U. S. Patent No. 3,652,589.

Because of the bitter taste of the tramadol active ingredient, the pellets may be coated for taste-masking purposes although this may be of less importance if the pellets are used in a capsule dosage form.

In a further embodiment, the invention provides unitary dosage forms, which comprise pellets as described herein in an amount that is such that the dosage form contains an effective amount of the active ingredient incorporated into the pellets. Examples of such dosage forms are sachets. A particular dosage form is a capsule.

In a particular embodiment, the invention provides unitary dosage forms, which comprise tramadol hydrochloride pellets as described herein in an amount that is such that the dosage form contains an effective amount of tramadol hydrochloride. Particular embodiments of such dosage forms may contain from about 10 mg to 100 mg tramadol hydrochloride per unit, preferably from about 15 mg to about 75 mg of tramadol hydrochloride per unit, or from about 25 mg to about 65 mg of tramadol hydrochloride per unit.

The dosage forms of the invention has a particular dissolution rate in vitro, said dosage forms providing an effective therapeutic effect for a sufficiently long period of time, in particular for at least 12 hours more in particular for about 24 hours after oral administration.

In particular the oral dosage forms of the invention are suited for dosing every 24 hours.

Examples

Example 1

A dry blend of 1400 mg of tramadol hydrochloride, 1400 mg of microcristalline cellulose and 1200 mg of glyceryl benehate (Compritol 888 ATO ™, Gattefosse) is wet massed with approximately 60 mg of water and extruded through a small orifice (approx. 1 mm). The extruded material is placed into a spheroniser where it is spun at high speed (pellet speed of between 5 and 20ms^{-2}). During this step the extrudate breaks and rounds into pellets, the size being determined by the size of the extrusion

orifice. It was found that the extrudate broke easily and produced round pellets of uniform size at a much reduced moisture level. No sticking was observed in the spheroniser and the pellets coated uniformly.

Example 2

Dissolution Rate:

The in vitro dissolution rate of the preparation of example 1 was measured according to Ph. Eur. Paddle Method (USP App. 2) at 75 rpm. The dissolution tests were performed on the capsules in 900 ml 0.05 M Phosphate buffer with a pH value of 6.8 (USP) at 37° C. We used sinker device to avoid the floating of the capsules in the vessel. The detection was performed by using the high performance liquid chromatography (HPLC) with a refractive index detector for the detection of the active compound. For an in situ measurement of the release rate, a fiber optic dissolution system was used, using the second derivative correction method at the wavelength range of 283 to 289 nm. The dissolution profile can be described as follows:

About10% Tramadol released after 1 hour,
About 25% Tramadol released after 2 hours,
About 45% Tramadol released after 4 hours,
About 67% Tramadol released after 8 hours,
About 80% Tramadol released after 12 hours,
About 90% Tramadol released after 18 hours
About 100% Tramadol released after 24 hours by weight.

What is claimed is:

1. Spherical pellets comprising a water-soluble active ingredient.

2. The pellets of claim 1 for application in sustained release products.

3. The pellets of claims 1 or 2 which pellets are coated.

4. The pellets of any of claims 1 – 3 wherein the active ingredient is tramadol.

5. A pharmaceutical dosage form containing spherical pellets as claimed in any of claims 1 – 3.

6. A dosage form according to claim 5 which is a capsule.

7. A dosage form according to claims 5 or 6 which is a sustained release oral pharmaceutical dosage form containing an effective amount of a water-soluble active ingredient, characterized in that the active ingredient is formulated into a spherical pellet, which has been coated with an appropriate sustained release coating.

8. A dosage form according to claims 5 – 7 wherein the active ingredient is tramadol, or a pharmaceutically acceptable acid addition salt thereof.

9. A process for manufacturing spherical pellets as claimed in any of claims 1 – 4, said method comprising extruding a mixture of the active ingredient with a suitable carrier in the presence of a dry lubricant and spheronizing the extrudate.

10. A process according to claim 9 wherein the dry lubricant is a triglyceride.

11. A process according to claim 10 wherein the pellets are subsequently coated with a suitable coating.

12. A process for manufacturing a pharmaceutical dosage from as claimed in any of claims 5 - 8, said method comprising filling the pellets into a suitable container.

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ABSTRACT

Spherical Pellet Formulations

This invention relates to spherical pellets containing a water-soluble drug, which pellets may be coated, and to sustained release oral dosage forms containing said pellets. The invention further relates to a process for preparing said pellets based on the use of a dry lubricant.